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(54) Title: HARD GELATIN CAPSULES WITH LOW WATER TRANSPORT AND PROCESS FOR THE PRODUCTION THEREOF			
(57) Abstract			
<p>The present invention provides a hard gelatin capsule with a reduced water transport or water vapour permeation through the hard gelatin capsule, wherein either a polymer layer is laminated on to a hard gelatin shell and/or at least one additive is added to a gelatin formulation during the hard gelatin capsule production.</p>			

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**Hard gelatin capsules with low water transport
and process for the production thereof**

10 The present invention is concerned with hard gelatin capsules with a low permeability to water vapour which reduce the sensitivity thereof to storage conditions and/or to hygroscopic fills and improves the protection of fills against atmospheric water vapour.

15 Hard gelatin capsules are widely used in the pharmaceutical industry as well as in the health food supplement market. The main use thereof is as dosage form for solid preparation, i.e. active materials and excipients in powder form.

20 An important limitation of the use of capsules results from an exchange of moisture between capsules and fills. Capsules generally contain about 10 to 16% by weight of water. This water content is function of the relative humidity (RH) of the surroundings. When capsules are filled and stored in a closed container, the moisture 25 will redistribute between the various components until a uniform relative humidity is attained in the vapor phase.

Another limitation is due to the high rate of water transport and/or high water vapor permeability through gelatin capsules shells. According to measurements which

we have made at ambient temperature with a difference of 50% in the relative humidity across a gelatin film of 100 μm thickness, the weight of water vapor permeating through the film during a period of 24 hours is about 5 twice the weight of the film itself. Consequently, when capsules exposed to an open environment, the fill will take up moisture from the environment by means of permeation and quickly attain a water content in equilibrium with the environment.

10 Both of the above gelatin characteristics can have an effect either on the capsules or on the fills or both.

15 Moisture changes in the capsules can have an effect on the mechanical stability of the gelatin capsules used as a container: if too humid, they become soft and may deform and if too dry, they may become brittle.

20 Moisture take-up by fills from capsules or more frequently from the environment by permeation may affect the properties of powder fills: they may agglomerate or, more seriously, degrade chemically for example by hydrolysis. Indeed, it is recommended to store most drugs in a dry environment.

25 A more recent development has enabled the filling of liquid products into hard gelatin capsules. Again and in a more acute way, the main limitation has been the high hygroscopicity of most of the recommended excipients.

30 Gelatin is by nature hygroscopic. It adsorbs water vapor, swells in water at low temperature and dissolves at high temperature. The high water solubility of capsules is essential for the administration thereof but also implies high water solubility (S) and diffusion parameters (D)

and a high water vapor permeability (P) as $P = SD$. The water contained in hard gelatin capsules is an element for the triple helix structure and acts as a most efficient plasticizer.

- 5 The hygroscopicity of gelatin and the moisture exchange between capsules and fills may be studied by sorption-desorption isotherms of gelatin capsules and fills. These studies are widely found in the literature, (see, in particular, K. Ito & al., Chem. Pharm. Bull. 17 (3), 1969
- 10 1134-1137 and M.J. Kontny & al., Int. J. Pharm. 54, 1989, 79-85). These authors report that, for a closed system, the final water content is intimately dependent upon the affinity of the various materials for water. Experimental equilibrium water content and relative humidity and
- 15 estimated values calculated from the isotherms of these materials were in good agreement with each other.

With regards to the water permeability of hard gelatin capsules, there are very few studies in the literature, reference being made to W.A. Strickland & al., J. Pharm. Sci., 51 (10) 1962, 1002-1005. These authors concluded that gelatin capsules offer little protection to a hygroscopic content from atmospheric water vapor. No significant attempt has been made to reduce the water vapor permeability of hard gelatin capsules. This could be explained by the fact that, in most cases, a reduction of the water vapor permeability is combined with a decrease in the hyrosolubility of gelatin capsules.

Consequently, it is an object of the present invention to overcome the disadvantages of the previously known hard gelatin capsules.

Thus, according to the present invention, there is provided a hard gelatin capsule with a reduced water vapour permeation through the hard gelatin capsule, wherein either a polymer is laminated on to a hard 5 gelatin shell and/or at least one additive is added to a gelatin formulation during the hard gelatin capsule production.

Thus, the present invention concerns hard gelatin capsules with a low water transport, these capsules being 10 laminated or containing additives.

Laminated capsules.

These capsules comprise a gelatin layer as base capsule material and a polymer layer with a low water permeability as barrier to the water transport.

15 These capsules can be manufactured by double dipping moulding or by coating techniques.

Double dipping comprises dipping into a gelatin solution to form a gelatin layer and another dipping into a polymer solution to form a polymer layer. A first dipping 20 into a gelatin solution followed by a second dipping into a polymer solution after drying of the first layer gives a hard gelatin capsule with a polymer layer on the outside. The other way round, dipping first into a polymer solution followed by a dipping into a gelatin 25 solution gives a hard gelatin capsule with a polymer layer on the inside.

The capsule coating comprises recovering of hard gelatin capsules with a polymer layer on the outside using conventional techniques for capsule or tablet coating.

The polymer layer is a polyvinyl alcohol which is water soluble, the solubility in water increasing as the molecular weight decreases. As is known, polyvinyl alcohol is prepared from polyvinyl acetate by replacement of the acetate groups by hydroxyl groups. According to the present invention, the polymer used is to be understood to include not only polyvinyl alcohol but also polyvinyl acetate, as well as partly or wholly hydrolysed polyvinyl acetate, a degree of hydrolysis of more than 80% being preferred.

Commercially available polyvinyl alcohols have degrees of hydrolysis of 98-99 mol % and of 87-89 mol %. Thus, they are partly saponified polyvinyl acetates with a residual content of acetyl groups of about 1 - 2 or 11 - 13 mol %, respectively.

Apart from the homopolymers, there can also be used copolymers with, for example, ethylene and/or vinyl chloride.

For the sake of simplicity, the polymer used is hereinafter referred to as PVA.

An aqueous solution of PVA can be used for dipping and coating to produce the desired laminate which does not affect the capsule hydro solubility. PVA has good film formability and it can easily be made into a thin layer either by dipping or coating. PVA has an extremely low water permeability which is more than 100 times lower than that of gelatin. Thus, PVA is a good barrier to water transport.

Although there is no limitation to the molecular weight of the PVA used, it is preferably higher than 10000.

The PVA can be used in the form of a solution in water or in a solvent, an aqueous solution being preferred. There is no limitation to the PVA concentration in the solution; it depends upon the viscosity required.

5 The thickness of the PVA layer is preferably from 1 to 50 % and more preferably 5 to 30 % of the total thickness of the capsule wall.

A setting agent such as SATIAGEL ME5 (Kappa carrageenan + KCl) supplied by Sanofi Bio-Industries can be added into 10 PVA solution in order to attribute the solution a suitable setting ability. The concentration of the setting agent is 0.05 % to 2 %, preferably 0.1 % to 0.8 %.

Capsules with additives.

15 In the case of these capsules, the gelatin contains, as additive, at least one polyol, which results in a significant reduction of the water vapour permeability. We have found that this permeability decreases with the additive content and that the rupture or dissolving times 20 of the capsules also decreases with increasing content of additive.

The polyols which can be used according to the present invention include sugars, sugar alcohols and other sugar substitutes, as well as polyvinyl alcohol, and structural 25 analogues thereof.

Sugars which can be used according to the present invention include monosaccharides, namely, aldohexoses (for example glucose, mannose and galactose), ketohexoses (for example fructose) and aldopentoses (for example

arabinose, xylose and ribose), as well as disaccharides (for example maltose, lactose and sucrose).

Sugar alcohols which can be used according to the present invention are polyols which can be obtained by the reduction of the carbonyl function of mono-saccharides, They include, for example, sorbitol, mannitol, lactitol, maltitol, glycerol, threitol, erythritol, adonitol, arabitol, xylitol, galactitol and structural analogues thereof.

10 According to the present invention, sugar substitutes are to be understood to mean polyols which can be used nutritionally as replacements for sugars, for example lactitol, isomalt, hydrogenated glucose and maltose syrups and fructooligosaccharides.

15 The additives are incorporated into hard gelatin capsules by addition to a gelatin solution to be used for capsule manufacture. These additives are hydrosoluble and compatible with gelatin and the addition does not result in a significant change in the setting ability of the 20 gelatin solution or in a detrimental change in the viscosity of the gelatin solution. Consequently, capsules containing these additives can be manufactured by conventional dip moulding process under standard conditions.

25 These additives not only greatly reduce the water permeability of gelatin capsules but also significantly reduce the hygroscopicity thereof and do not affect the dissolution in water.

The amount of the additive content in the gelatin can be from 1 to 50 %, preferably 5 to 40 % or and more preferably from 10 to 30 %.

5 The gelatin capsules according to the present invention can contain one or more of the additives.

10 The gelatin used for the production of capsules according to the present invention can be coloured with dyes and/or pigments, can contain opacifiers, preservatives and plasticisers. Substances can also be added to aid the manufacturing process and also to aid the subsequent 15 performance of the capsules.

20 The addition of dyes and/or pigments as colouring agents to the gelatine used provides aesthetic and psychological effects on the patient, serves for identification purposes and can provide light protection, which is of 25 importance when the capsules contain photosensitive materials. The colouring agents used must, of course, be pharmaceutically acceptable and include, for example, synthetic water-soluble dyes, such as azo, indigoid, quinophthalone, triphenylmethane and xanthene dyes, as well as certain dyes of natural origin, for example carotenoids and flavones, and also pigments, for example titanium dioxide which acts as an opacifying agent, carbon and iron oxides.

30 Since gelatin is a good medium for bacterial and fungal growth, it is advisable to add to the gelatin one or more bactericidal, bacteriostatic and fungicidal agents, usually in a concentration of up to 0.2 % w/w. One preferred combination for this purpose contains methyl and propyl hydroxybenzoates in a ratio of 4:1. The use of certain non-toxic organic acids, for example benzoic,

propionic and sorbic acids, preferably in the form of a water-soluble salt, provides a protection against moulds and yeasts and also imparts bacteriostatic properties. They are usually employed in concentrations of up to 1 % w/w.

For the production of the capsules, the use of plasticisers, lubricants and colouring agents of pharmaceutical quality leads to optimum product qualities.

10 Pharmacologically acceptable plasticisers, such as polyethylene glycol, or preferably low molecular weight organic plasticisers, such as glycerol, dioctyl sodium sulphosuccinate, triethyl citrate, tributyl citrate, 1,2-propyleneglycol, mono-, di- or triacetates of glycerol
15 and the like, are used in various concentrations of about 0.5 to 40 % and preferably of 0.5 to 10 %, based on the weight of the polymer.

Pharmacologically acceptable lubricants, such as sodium lauryl sulfate, the stearates of aluminium, calcium, magnesium and tin, as well as talc, silicones and the like, can be used in concentrations of about 0.1 to 10 % and preferably of 0.1 to 5 %, referred to the weight of the polymer.

20 For the production of aesthetic effects, for identification purposes, for psychological effects on patients and also for light protection, pharmaceutically acceptable colouring agents, such as azo dyes, and other dyestuffs and pigments, such as iron oxides, titanium dioxide, natural dyes and the like, are used in concentrations of about 0.001 to 10 % and preferably of 0.001 to 5 %, referred to the weight of the polymer.

In addition, we have found that capsules according to the present invention can be produced with various grades of gelatin combined with 5 to 95 % by weight of extenders, such as sunflower proteins, soya bean proteins, cotton 5 seed proteins, peanut proteins, rape seed proteins, lactose, gum arabic, acrylates and methacrylates, water-soluble derivatives of cellulose, such as cellulose acetyl phthalate (CAP), hydroxy-propylcellulose, hydroxypropylmethylcellulose, hydroxy-propylmethyl 10 cellulose phthalate (HPMCP), hydroxy-methylcellulose, polyvinylpyrrolidone, shellac, bentonite, polyvinyl acetate phthalate, phthalated gelatin, succinated gelatin and polysaccharides, such as agar-agar.

15 The manufacture of capsules with the use of plasticisers, lubricants and colouring agents, preferably of pharmaceutical quality, leads to optimum product qualities.

20 The capsules according to the present invention can be used as containers especially for the exact dosing of nutrients, medicaments, chemicals, colouring materials, spices, fertilizer combinations, seeds and seed materials, cosmetics and agricultural products. In particular, the capsules can be used as containers for hygroscopic materials and for inhalation agents. They can 25 also be used as matrices of the most varied forms and sizes for nutrients, medicaments, chemicals, colouring materials, spices, fertilizer combinations, seeds and seed materials, cosmetics and agricultural products. The capsules according to the present invention can also 30 contain tablets or so-called caplets (tablets pressed in capsule form), as well as with special forms, for example microdispersions within the matrix which are liberated from the matrix by breakdown and/or dissolving and/or bioerosion and/or diffusion and consequently be

liberation-controlled systems for the administration of the enclosed substances. Furthermore, the capsules can be filled with medicinal or surgical products formed from appropriate masses or foams thereof.

5 Test for the water vapor permeability of capsules.

The water vapor permeability of capsules is evaluated by the moisture uptake kinetics of a hygroscopic powder filled into the capsules. Capsules were first equilibrated at 22°C/50% relative humidity, the 10 hygroscopic powder used being the sodium salt of carboxymethyl-cellulose (CMC), with high viscosity (from Sigma). The CMC which has an equilibrium water content of about 16 % at 22°C/50% relative humidity was previously dried at 105°C to reduce the water content thereof to 15 zero. After filling with CMC and closing, the capsules are stored at 22°C/50% relative humidity and the weight thereof was monitored from time to time in order to determine the take-up of moisture by the CMC. The CMC water content was calculated from the weight increase of 20 the filled capsules. Taking into account the mean wall thickness of the capsules and the initial dry CMC weight, a mathematical determination of the comparative permeability of different capsules can be carried out from the CMC moisture uptake kinetics.

25 Test for the water vapor permeability of films.

The water vapor permeability of films was determined under stable permeation at 22°C by means of a permeation cell. This cell had a permeation window covered with the film to be tested. Filling the cell with freshly 30 regenerated silica gel (from Prolabo) and storing at 22°C/50% relative humidity creates a difference in the

vapor pressure across the film and thus promotes a water vapor permeation across the film. As the permeated water vapor is taken up by the silica gel, the amount of the first W (g) can be determined from the weight increase of 5 the second. From the film thickness L (μm) and area A (m^2), permeation time t (h) and vapor pressure difference p (mmHg), the permeability is calculated from:

$$P = WL/At\Delta p \ (\text{g} \cdot \mu\text{m}/\text{m}^2 \cdot \text{h} \cdot \text{mmHg}).$$

10 The following examples are given for the purpose of illustrating the present invention:

Laminated capsules.

Example 1.

15 To 3.6 liters of demineralized water with a temperature of about 60°C were added and dissolved 18 g of SATIAGEL ME5 (0.5% by weight). Into the solution was introduced 400 g of PVA 15000 with a degree of hydrolysis of 86 to 89% from Fluka (10% by weight) which was dissolved with stirring over the course of more than 5 hours.

20 The PVA solution obtained was introduced into the dipping dish of a pilot dipping machine, the solution temperature being maintained at 55°C. A first dipping into the PVA solution with pins of hard capsule size No. 1 was carried out in the conventional way. After drying the PVA layer, 25 a second dipping into a gelatin solution, made with a mixture of pharmaceutical grade gelatins of types A and B with Bloom above 200 g, according to conventional methods gave capsules internally laminated with PVA which were tested for water vapor permeability with reference to conventional hard gelatin capsules by using the above-

described test for the water vapour permeability of capsules.

Table 1

		ref. capsules	capsules internally laminated with PVA
5		capsules	
	PVA layer thickness (μm)	0	8
	total wall thickness (μm)	108	115
10	PVA/total (%)	0	7
	comparative permeability	100	15

Table 2

	time (hours)	0	3	20	50	100	200
15	CMC water content in ref. capsule (%)	0	1.7	8.0	13.2	14.8	15.2
	CMC water content in laminated capsule (%)	0	0.3	1.7	3.8	6.6	10.2

Example 2.

A PVA solution was prepared as in Example 1. The dish temperature of the PVA solution was maintained at 45°C. A first dipping into the PVA solution and a second dipping into the gelatin solution were carried out as in Example 1 to give capsules internally laminated with PVA.

Table 3

	ref. capsules	capsules internally laminated with PVA
5		
PVA layer thickness (μm)	0	15
total wall thickness (μm)	108	114
PVA/total (%)	0	13
comparative permeability	100	11

10 Table 4

time (hours)	0	3	20	50	100	200
CMC water content in						
ref. capsule (%)	0	1.7	8.0	13.2	14.8	15.2
CMC water content in						
15 laminated capsule (%)	0	0.2	1.3	3.0	5.3	8.4

Example 3.

A PVA solution was prepared as in Example 1. The dish temperature of the PVA solution was maintained at 45°C. A first dipping into the gelatin solution and a second dipping into the PVA solution gave capsules externally laminated with PVA.

Table 5

	ref. capsules	capsules externally laminated with PVA
5		
PVA layer thickness (μm)	0	14
total wall thickness (μm)	108	115
PVA/total (%)	0	12
10 comparative permeability	100	11

Table 6

	time (hours)	0	6	30	50	100	200
15	CMC water content in						
ref. capsule (%)	0	2.3	8.0	11.4	14.5	15.6	
CMC water content in							
laminated capsule (%)	0	0.2	1.1	2.0	3.8	6.5	
Capsules with additive.							

Example 4.

20 The properties of gelatin films with additive were first studied. The gelatin films were cast from a 27% (w/w) gelatin solution containing various additives with contents from 0 % to 30 % [w(additive)/w(gelatin)]. Films were dried under atmospheric conditions (22°C/50% relative humidity) for 24 hours and evaluated for the water vapor permeability, hygroscopicity and dissolution thereof. The results obtained are summarised in the following Tables 7 to 9.

Table 7

Water vapor permeability of gelatin films (g . $\mu\text{m}/\text{m}^2 \cdot \text{h}$. mmHg)

	additive	0	5%	10%	15%	20%	25%	30%
5	sorbitol	81	28	14	7.0	4.5	3.5	3.2
	mannitol	91		17		5.4		2.8
	xylitol	91		16		5.8		5.1
	glucose	73		17		5.1		2.0
	lactose	78		39		19		10
10	sucrose	92	68	40				
	maltitol	91		27		8.1		3.4
	glycerol	95	47	33		2.1		
	fructose	84		16		4.1		1.6

Table 8

15 Water content (%) of gelatin films in equilibrium at
22°C/50% relative humidity

	additive	0	5%	10%	15%	20%	25%	30%
20	sorbitol	15.1	13.5	12.5	11.8	11.2	11.0	10.7
	mannitol	15.1		12.8		11.5		11.0
	xylitol	15.1		12.6		11.4		11.0
	glucose	15.1		14.5		13.5		13.8
	lactose	15.3		14.5		13.5		12.8
25	sucrose	15.0	14.4	13.6				
	maltitol	15.6		13.4		12.0		11.1
	glycerol	15.0	13.5	12.3		11.8		
	fructose	15.7		14.3		13.4		13.5

Table 9

Rupture time (s) of gelatin films in water at 37°C								
	additive	0	5%	10%	15%	20%	25%	30%
5	sorbitol	166	176	139	136	110	106	98
	mannitol	168		123		98		94
	xylitol	168		120		97		85
	glucose	169		127		121		99
10	lactose	160		131		121		106
	sucrose	164	168	156				
	maltitol	157		135		111		106
	glycerol	159	164	127		110		
15	mannitol	160		121		111		93

Example 5.

Gelatin films with a mixture of additives (sorbitol + mannitol) of 20% were cast and tested as described in Example 4.

Table 10

	sorbitol	20%	15%	10%	5%	0%	0%
	mannitol	0%	5%	10%	15%	20%	0%
20	permeability (g.μm/m ² .h.mmHg)	4.3	6.0	4.4	4.4	4.7	96

Example 6.

To 80 litres of 32% (w/w) gelatin solution were added 2.8 kg of sorbitol, (10% w (sorbitol) /w (gelatin)), or 3.2 kg of sorbitol (15%), previously dissolved in water (60%). The viscosity and temperature of the gelatin

solution obtained were then adjusted according to the conventional dipping production process. Size No. 1 transparent capsules containing 10% and 15% sorbitol were produced on a conventional production machine.

5 **Table 11**

		ref. capsules	capsules with	capsules
		with		
		(transparent)	10% sorbitol	15% sorbitol
Capsules mean				
10	weight (mg)	76	74	75
comparative permeability		100	20	11

Table 12

		time (hours)	0	4	24	50	100	166
15	191							
	CMC water content (%)							
	in ref. capsule	0	2.1	8.4	13.1	15.0	15.5	
	15.6							
	CMC water content (%)							
20	in capsules with 10%							
	sorbitol	0	0.5	2.3	4.3	7.2	10.0	
	10.9							
	CMC water content (%)							
	in capsules with 15%							
25	sorbitol	0	0.2	1.2	2.4	4.4	6.4	
	7.1							

Example 7.

To 60 litres of 32% gelatin solution were added 1.05 kg (5%) or 2.1 kg (10%) of sorbitol and 0.42 kg of titanium

dioxide (TiO_2). The viscosity and temperature of the gelatin solution obtained were adjusted according to conventional dipping production processes. Size No. 1 opaque capsules containing 5% and 10% of sorbitol were produced on a conventional production machine.

Table 13

	ref. capsules with with	capsules with	capsules
	(opaque)	5% sorbitol	10%
10	sorbitol		
	Capsules mean		
	weight (mg)	76	75
	comparative		78
	permeability	100	49
			23

15 Table 14

time (hours)	0	5	22	50	76	142
150						
CMC water content (%)						
in ref. capsule	0	2.3	7.6	12.9	14.6	16.0
20 16.0						
CMC water content (%)						
in capsules with 5%						
sorbitol	0	1.1	4.2	8.5	11.0	14.6
14.7						
25 CMC water content (%)						
in capsules with 10%						
sorbitol	0	0.5	2.0	4.4	6.2	9.7
10.0						

Claims

1. A hard gelatin capsule with a reduced water transport or water vapour permeation through the hard gelatin capsule, wherein either a polymer layer is laminated on to a hard gelation shell and/or at least one additive is added to a gelatin formulation during the hard gelatin capsule production.
5. 2. A hard gelatin capsule according to claim 1, wherein the polymer lamination is internal and/or external.
10. 3. A hard gelatin capsule according to claim 1 or 2, wherein the polymer used for the lamination is selected from the group consisting of polyvinyl alcohol, polyvinyl acetate, partly and wholly hydrolysed polyvinyl acetate and co-polymers thereof.
15. 4. A hard gelatin capsule according to any of the preceding claims, wherein the polymer layer represents 1 to 50% of the total thickness of the capsule wall.
20. 5. A hard gelatin capsule according to claim 4, wherein the polymer layer represents 5 to 30% of the total thickness of the capsule wall.
6. A hard gelatin capsule according to any of the preceding claims, wherein the additive used is a polyol.

7. A hard gelatin capsule according to claim 6, wherein the polyol is a sugar, sugar alcohol, sugar alcohol ester, a sugar substituted or polyvinyl alcohol or a structural analogue thereof.
- 5 8. A hard gelatin capsule according to claim 7, wherein the sugar is a monosaccharide or a disaccharide.
9. A hard gelatin capsule according to any of claims 6 to 8, wherein the polyol is selected from the group consisting of sorbitol, mannitol, xylitol, maltitol, 10 glycerol, glucose, lactose, sucrose and fructose and the structural analogues thereof.
10. A hard gelatin capsule according to any of the preceding claims, wherein the amount of the additive content in the gelatin is from 1 to 50% by weight.
- 15 11. A hard gelatin capsule according to claim 10, wherein the amount of the additive content in the gelatin is from 5 to 40%.
12. A hard gelatin capsule according to claim 11 wherein the amount of additive content in the gelatin is from 20 10 to 30%.
13. Process for the production of a hard gelatin capsule according to claim 1, wherein a hard gelatin capsule is produced in conventional manner and then laminated internally and/or externally with the polymer by a 25 dipping or coating technique and/or wherein the additive is added to a gelatin formulation and a hard

gelatin capsule is produced from said formulation in conventional manner, whereafter, if desired, the hard gelatin capsule so produced is laminated internally and/or externally with the polymer.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 96/03263A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 816 259 (JAMES W. MATTHEWS) 28 March 1989 see claims 9,12 see column 3, line 55 - line 60 see column 5; example 2 ---	1-3,6-13
X	US,A,3 467 748 (R. P. SCHERER) 16 September 1969 see claims 1,4 see column 3; examples 1-3 ---	1-3,6-13
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 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Ventura Amat, A

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 180 287 (SHIN-ETSU CHEMICAL CO) 7 May 1986 see claims 1,7 see page 4, line 1 - page 5, line 2 -----	1-13

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